

Amendment B  
U.S. Appl. 09/888,008  
June 28, 2004

### Remarks

#### Claim Amendments

Claims 1-2, 7 and 11-15 are amended in this Amendment B. Claims 10 and 16-21 are canceled. Upon entry of the amendment, claims 1-9 and 11-15 will be pending in the application.

Claims 1, 2 and 13 have been amended to more particularly define the invention and to improve the form of the claims. In particular, the amended claims require that the coupling and detecting steps of the method of the present invention are performed "sequentially without removing the substrate or product that is not coupled to the resin." No new matter has been added. The amended claims are supported in the specification, for example, at page 2, lines 25-29; page 3, lines 4-6 and page 3, lines 13-21.

Claim 7 has been amended to include proper Markush language.

Claims 12 and 14 have been amended to more particularly define the enzymes used in the present invention. No new matter has been added. The amended claims are supported by page 7, lines 11-21 of the specification.

Claim 15 has been amended to correct obvious typographical errors and to improve the form of the claim.

Claims 10 and 16-21 have been cancelled. Applicants reserve the right to pursue any canceled subject matter and/or any other subject matter disclosed in this application in one or more later-filed divisional and/or continuation applications.

#### Rejection under 35 U.S.C. §102(b)

Claims 1-3, 5-6, 8-11 and 13 stand rejected under 35 U.S.C. §102(b) as anticipated by Cerretani et al. Reconsideration and withdrawal of the rejection is requested for the reasons set forth below.

As described in the specification at page 2, lines 25-29, the present invention is directed to methods for determining enzyme activity using a sensitive and reliable assay which can stop the reaction and separate the enzyme product from the substrate for detection and quantification in a single step. Such methods have the advantage of being adaptable for automated, high-

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throughput formats as the assay may be used in a single reaction container without the need for multiple process steps. For example, amended claims 1, 2 and 13 are directed to a methods wherein (1) a compound selected from the group consisting of enzymes, enzyme fragments and abzymes is contacted with a labeled substrate to form a differentially-charged product; (2) either the substrate or the differentially-charged product is selectively coupled to an ion-exchange resin and (3) the label is detected and quantitated to determine the amount of substrate remaining or differentially-charged product formed. Each of the methods are further characterized in that the steps of coupling and detecting are performed sequentially without removing the substrate or product that is not coupled to the resin.

The cited reference, Cerretani et al. (Analytical Biochem), describes a specific radiometric assay for Hepatitis C virus NS3 protease. In particular, the reference describes cleaving a labeled Pep4AB substrate with an NS3 protease to form an N-terminal product of negative charge and a C-terminal product of positive charge. An ion exchange resin is then added to solution to capture the negatively charged species, which were removed from solution by centrifugation. The positive-charged species remaining in solution are then counted to determine the activity of the NS3 protease. However, nothing in the reference describes that the assay can be completed without removing the negatively charged product that is coupled to the resin. Because the references do not describe a method wherein the steps of coupling and detecting are performed sequentially without removing the substrate or product that is not coupled to the resin as required by amended claims 1, 2 and 13, it is respectfully submitted that claims 1, 2 and 13 are patentable over Cerretani et al. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

It is respectfully submitted that claims 3, 5-6 and 8-11, which depend from and further limit claims 1 and 2, are not anticipated by the cited reference for the reasons stated above with respect to claims 1 and 2. Reconsideration and withdrawal of the rejection is respectfully requested.

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**Rejection under 35 U.S.C. §103(a)**

Claims 4, 7, 12 and 14-15 stand rejected under 35 U.S.C. §103(a) as obvious over Cerretani et al in view of each of Sandmann (Physiologia Plantarum) and Strulovici, U.S. Patent No. 5,759,787. Reconsideration and withdrawal of the rejection is respectfully requested.

As described above, the present invention is directed to methods for determining enzyme activity using a sensitive and reliable assay which can stop the reaction and separate the enzyme product from the substrate for detection and quantification in a single step. Such methods have the advantage of being adaptable for automated, high-throughput formats as the assay may be used in a single reaction container without the need for multiple process steps.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of prior art references. Further, the references, when combined, must teach all of the claim limitations. See MPEP 2143. As described above, nothing in the primary reference, Cerretani et al., remotely teaches or suggests an assay which can be completed in a single step without removing the substrate or product that is not coupled to the resin as required by amended claims 1, 2 and 13. Further, it is respectfully submitted that the deficiencies of the primary reference cannot be overcome by resorting to the teachings of Sandmann or Strulovici. Sandmann describes kinase enzyme assays wherein labeled substrates are reacted and separated by anion exchange chromatography and Strulovici describes kinase assays prepared on microtiter plates. However, nothing in the additional references remotely teaches or suggests a one-step assay taught in the present specification. Thus, it is respectfully submitted that the cited references, either alone or in combination, do not teach or suggest all of the limitations of claims 4, 7, 12 and 14-15, which depend from and further limit claims 1, 2 and 13. Accordingly, Applicants respectfully submit that claims 4, 7, 12 and 14-15 are patentable over Cerretani et al. in view of each of Sandmann and Strulovici.

**Rejection under 35 U.S.C. §112, first paragraph**

Applicants respectfully request reconsideration of the rejection of claim 15 as containing subject matter which was not described in the specification in such a way as to enable one skilled

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in the art to which it pertains to make and/or use the invention. Claims 16-21 have been canceled thereby mooting their rejection.

In order to be enabled under 35 U.S.C. §112, first paragraph, "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Questions of enablement are evaluated against the claimed subject matter and the first analytical step requires a determination of exactly what subject matter is encompassed by the claims. See, MPEP 2164.08. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In the instant case, claim 15 is taught at page 10, lines 1-10 of the specification. In particular, Applicants describe the use of the assay of the invention in screening for compounds or compositions that selectively affect enzyme activity. Accordingly, it is respectfully submitted that claim 15, which is directed to a method for identifying a molecule, compound or composition that affects the activity of an enzyme, is commensurate in scope with the teachings in the specification and the general knowledge available to one of ordinary skill in the art. Thus, claim 15 is sufficiently enabled under 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

**Rejection under 35 U.S.C. §112, second paragraph**

Applicants respectfully request reconsideration of the rejection of claims 1-21 as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Each of the deficiencies of the claims have been addressed as follows:

1. Claims 1, 2 and 13 have been amended to require the more definite step of "detecting and quantitating the label to determine . . . ."
2. Claim 10 has been canceled.
3. Claim 11 has been amended to remove the phrase "said high-throughput."
4. Claims 12 and 14 have been amended to provide the names of the enzymes where appropriate.

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5. Claim 15 has been amended to correctly spell "isozyme" and "affects."

6. Claims 18 and 19 have been canceled.

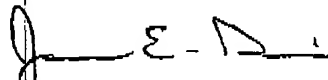
It is respectfully submitted that each of the above-described amendments obviate the objections to the claims under 35 U.S.C. §112, second paragraph.

**Conclusion**

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (314) 446-7683.

The Commissioner is hereby authorized to charge \$110.00 for the purchase of a one-month extension of time under 37 C.F.R. 1.136(a) to Deposit Account No. 08-0750. Further, if there is ever any other fee deficiency or overpayment in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. 08-0750.

Respectfully submitted,



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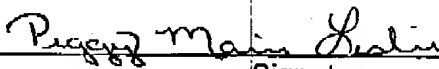
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Amendment B (9 pages)

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